

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup>:</b> <b>A61K 9/14, 9/22</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 97/16172</b> <b>(43) International Publication Date:</b> 9 May 1997 (09.05.97)
<b>(21) International Application Number:</b> PCT/US96/17991 <b>(22) International Filing Date:</b> 4 November 1996 (04.11.96) <b>(30) Priority Data:</b> 08/553,008 3 November 1995 (03.11.95) US <b>(71) Applicant:</b> EDWARD MENDELL CO., INC. [US/US]; 2981 Route 22, Patterson, NY 12563 (US). <b>(72) Inventors:</b> BAICHWAL, Anand, R.; 5 Kendell Drive, Wappinger Falls, NY 12590 (US). McCALL, Troy, W.; 4 Sullivan Farm, New Milford, CT 06776 (US). <b>(74) Agents:</b> RASKIN, Martin, G. et al.; Steinberg, Raskin & Davidson, P.C., 1140 Avenue of the Americas, New York, NY 10036 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> CONTROLLED RELEASE FORMULATION (ALBUTEROL)  <b>(57) Abstract</b>  A sustained release pharmaceutical formulation and methods of making and using the same are provided. The sustained release pharmaceutical formulation includes a sustained release excipient including a gelling agent, an inert pharmaceutical diluent, an optional hydrophobic material and/or hydrophobic coating, and a medicament for sustained oral administration.		

BEST AVAILABLE COPY

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

5

CONTROLLED RELEASE FORMULATION (ALBUTEROL)FIELD OF THE INVENTION

10           The present invention relates to controlled  
release formulations which may be blended with a wide  
range of therapeutically active medicaments and made  
into controlled release solid dosage forms for oral  
administration.

15

BACKGROUND OF THE INVENTION

          The advantages of controlled release products are  
well known in the pharmaceutical field and include the  
ability to maintain a desired blood level of a  
20       medicament over a comparatively longer period of time  
while increasing patient compliance by reducing the  
number administrations. These advantages have been  
attained by a wide variety of methods. For example,  
different hydrogels have been described for use in  
25       controlled release medicines, some of which are  
synthetic, but most of which are semi-synthetic or of  
natural origin. A few contain both synthetic and  
non-synthetic material. However, some of the systems  
require special process and production equipment, and  
30       in addition some of these systems are susceptible to  
variable drug release.

          Oral controlled release delivery systems should  
ideally be adaptable so that release rates and profiles  
can be matched to physiological and chronotherapeutic  
35       requirements. In U.S. Patent Nos. 4,994,276,  
5,128,143, and 5,135,757, hereby incorporated by

5 reference in their entireties, it is reported that a  
controlled release excipient which is comprised of a  
synergistic combination of heterodisperse  
polysaccharides (e.g., a heteropolysaccharide such as  
xanthan gum in combination with a polysaccharide gum  
10 capable of cross-linking with the heteropolysaccharide,  
such as locust bean gum, in an aqueous environment) is  
capable of being processed into oral solid dosage forms  
using either direct compression (i.e., dry  
granulation), following addition of drug and lubricant  
15 powder, conventional wet granulation, or a combination  
of the two. The release of the medicament from the  
formulations therein proceeded according to zero-order  
or first-order mechanisms.

The controlled release excipients disclosed in  
20 U.S. Patent Nos. 4,994,276, 5,128,143, and 5,135,757  
are commercially available under the trade name TIMERx®  
from Edward Mendell Co., Inc., Patterson, N.Y., which  
is the assignee of the present invention.

European Pat. No. 234670 B describes a controlled-  
25 release pharmaceutical formulation containing xanthan  
gum wherein the xanthan gum comprises from about 7.5 to  
about 28 percent, by weight, of the formulation except  
for a formulation wherein the controlled release  
carrier comprises a mixture of 15-50 parts by weight  
30 dimethylsiloxane, 30-100 parts by weight silicic acid,  
30-100 parts by weight mannans or galactans or a  
mixture thereof, 50-150 parts by weight xanthans and 5-  
75 parts by weight micronized seaweed.

However, heretofore there has been no teaching of  
35 a controlled release formulation providing a novel and  
unexpected combination of suitable proportions of a  
homopolysaccharide such as, e.g., xanthan gum, a

5 heteropolysaccharide, such as, e.g., locust bean gum,  
together with an inert diluent and a pharmacologically  
acceptable hydrophobic material, so as to provide an  
improvement in controlled release properties for such  
an active medicament.

10

#### OBJECTS AND SUMMARY OF THE INVENTION

It is therefore an object of the present  
invention to provide a controlled release formulation  
for a therapeutically active medicament.

15

It is a further object of the present invention to  
provide a method for preparing a controlled release  
formulation for a therapeutically active medicament.

20

It is yet another object of the present invention  
to provide a controlled release excipient which may be  
used in the preparation of a sustained release oral  
solid dosage form of a therapeutically active  
medicament that provides an even rate of release of an  
active medicament.

25

It is a further object of the present invention to  
provide a controlled release excipient which, when  
combined with an effective amount of a bronchodilator,  
such as albuterol, is suitable for providing a  
sustained release of that medicament so as to provide a  
therapeutically effective blood level of the medicament  
for e.g., 12 or 24 hours, without allowing an excessive  
early release of medication, and where the release  
kinetics are unaffected by the contents of the  
patient's gastrointestinal tract.

30

It is yet a further object of the present  
invention to provide a method for treating patients  
with an active medication in controlled release form.

35

The above-mentioned objects and others are

5       achieved by virtue of the present invention, which  
relates in-part to a controlled release formulation  
comprising a therapeutically effective amount of a  
medicament, and a controlled release excipient  
comprising a gelling agent and a swelling agent, such  
10       as, for example, a homopolysaccharide, a  
heteropolysaccharide, an inert diluent.

In certain preferred embodiments of the invention,  
the ratio of the heteropolysaccharide gum to the  
homopolysaccharide gum is from about 1:3 to about 3:1.  
15       More preferably, the ratio is about 1:1. Preferably,  
the heteropolysaccharide gum includes xanthan gum and  
the homopolysaccharide gum includes locust bean gum.

The present invention is also related to a  
sustained release oral solid dosage form for albuterol  
or salts or derivatives thereof in an amount necessary  
20       to render a therapeutic effect in a human patient. The  
albuterol is present in an amount ranging from, e.g.,  
about 2 through about 50% by weight of the total  
formulation, or preferably from about 1 through about  
25       10% by weight or more preferably from about 1 through  
about 6% by weight of the total formulation.

The dosage form includes an inert pharmaceutical  
diluent so that the ratio of the inert diluent to the  
gelling agent is from about 1:8 to about 8:1.  
30       Preferably, the diluent is from the group consisting of  
a pharmaceutically acceptable saccharide, polyhydric  
alcohol, a pre-manufactured direct compression diluent,  
and mixtures of any of the foregoing. The diluent can  
also be a saccharide such as sucrose, dextrose,  
35       lactose, microcrystalline cellulose, fructose, xylitol,  
sorbitol, a starch, and mixtures thereof.

5           The dosage form optionally includes a  
pharmaceutically acceptable hydrophobic material. Any  
pharmaceutically acceptable hydrophobic material may be  
suitably employed. Suitable hydrophobic materials  
include carboxymethylcellulose, cellulose acetate  
10   phthalate, polyvinyl acetate phthalate, hydroxypropyl-  
methylcellulose phthalate, ethylcellulose, a copolymer  
of acrylic and methacrylic and esters, waxes, shellac,  
zein, hydrogenated vegetable oils, and mixtures of any  
of the foregoing. Preferably, the hydrophobic material  
15   selected from cellulose ether, a cellulose ester and an  
alkylcellulose, such as ethylcellulose and  
carboxymethylcellulose. The hydrophobic material may  
be included in the dosage form in an amount effective  
to slow the hydration of the gelling agent when exposed  
20   to an environmental fluid.

          The hydrophobic material is preferably present in  
an amount ranging from about 1 through about 90%, by  
weight, of the solid dosage form, and can also be  
present in an amount ranging from about 25% through  
25   about 50%, by weight, of the solid dosage form.

          The medicament can be any medicament for which an  
orally administered controlled release form is desired.  
Preferably, the formulation is prepared to include a  
pharmaceutically effective amount of albuterol or a  
30   salt or derivative thereof.

          The controlled release solid dosage form can be  
prepared in any conventional orally administered dosage  
form, including a tablet, as a granular form and as a  
granular form administered in a gelatin capsule  
35   containing a sufficient amount of the granules to  
provide an effective dose of the included  
therapeutically active medicament. For a tablet dosage

5 form, at least part of a surface of the tablet can  
optionally be coated with a hydrophobic material to a  
weight gain from about 1 to about 20 percent, by  
weight. Further, a granular dosage form can optionally  
10 be coated with a hydrophobic coating material to a  
weight gain that ranges from about 1% to about 20%.  
The hydrophobic material can be selected from, e.g., a  
cellulose ether, a cellulose ester and an  
alkylcellulose. The hydrophobic material can  
optionally be applied before, during or after the  
15 process of tableting. In addition, if there is a need  
for an early release of the active medicament, the  
coating can optionally be formulated to include from  
about 10 to about 40 percent of the total amount of the  
active medicament in a quick release external layer.

20 The invention also relates to methods for  
preparing a controlled release solid dosage form as  
described above for providing an active medicament in  
an amount effective for treating a patient for from 12  
to about 24 hours. The method includes the steps of  
25 preparing a sustained release excipient comprising from  
about 10 to about 99 percent by weight of a gelling  
agent comprising a heteropolysaccharide gum and a  
homopolysaccharide gum capable of cross-linking said  
heteropolysaccharide gum when exposed to an  
30 environmental fluid, the ratio of said  
heteropolysaccharide gum to said homopolysaccharide gum  
being from about 1:3 to about 3:1, and from about 0 to  
about 89 percent by weight of an inert pharmaceutical  
diluent, and optionally from about 1 to 90% by weight  
35 of a pharmaceutically acceptable hydrophobic material;  
and adding an effective amount of a medicament to  
provide a final product having a ratio of medicament to



5       gelling agent from about 1:3 to about 1:8, so that a  
gel matrix is created.

          The medicament to be added is preferably albuterol  
or salts or derivatives thereof in an amount ranging  
from, e.g., about 2 to about 50% by weight of the total  
10       formulation, or preferably from about 1 to about 10% by  
weight or more preferably from about 1 to about 6% by  
weight of the total formulation.

          The resulting mixture of the sustained release  
15       excipient preferably includes from about 10 to about 75  
percent gelling agent, from about 0 to about 90%  
hydrophobic material and from about 30 to about 75  
percent inert diluent. Thereafter, the dosage form can  
be tableted, granulated with a pharmaceutically  
20       acceptable hydrophobic material or placed in gelatine  
capsules. Optionally the tablet can be coated with a  
hydrophobic coating to a weight gain from about 1% to  
about 20%.

          Preferably, the medicament is albuterol or a salt  
25       or derivative thereof in an amount effective to provide  
therapeutically effective blood levels of said  
medicament for at least 24 hours.

          The present invention is further related to a  
method of treating a patient comprising orally  
30       administering the sustained release albuterol tablets  
to a patient, thereby providing therapeutically  
effective blood levels of the medicament for at least  
about 24 hours.

          By "sustained release" it is meant for purposes of  
35       the present invention that the therapeutically active  
medicament is released from the formulation at a  
controlled rate such that therapeutically beneficial

5 blood levels (but below toxic levels) of the medicament are maintained over an extended period of time, e.g., providing a 24 hour dosage form.

The term "environmental fluid" is meant for purposes of the present invention to encompass, e.g., an aqueous solution, such as that used for in-vitro dissolution testing, or gastrointestinal fluid.

10 In one aspect the invention provides formulations having particular pharmacokinetic properties. Thus, simply by way of example, the invention provides formulations suitable for oral administration that, when orally administered to a patient, provide a medicament plasma concentration-time curve with an area under the curve-calculated to infinity ("AUC<sub>∞</sub>"), ranging from about 89 to about 150 (ng-hours/ml) or even from about 112 to about 129 (ng-hours/ml). Further, the formulations according to the invention can provide, e.g., an AUC<sub>∞</sub> ranging from about 57 to about 157 (ng-hours/ml) (fasting patient) or from about 75 to about 162 (ng-hours/ml) (fed patient).

25 In addition, for example, mean peak plasma concentrations (C<sub>max</sub>) ranging from about 7 to about 12 ng/ml or even from about 9.5 to about 12 ng/ml. are provided. Further, the formulations according to the invention can provide, e.g., a C<sub>max</sub> ranging from about 4.5 to about 19 ng/ml (fasting patient) or from about 6 to about 16 ng/ml (fed patient).

35 In another example, time to mean peak plasma concentration (T<sub>max</sub>) ranging from about 3 to about 10 hours or even from about 3.5 to about 8 hours are provided. Further, the formulations according to the invention can provide, e.g., a T<sub>max</sub> ranging from about 3 to about 6 hours (fasting patient) or from about 3 to

5       about 8 hours (fed patient).

      In a further example, the formulation according to the invention provides, for example, ratios of AUC<sub>0-8</sub> (fasting patient) to AUC<sub>0-8</sub> (fed patient) that range from about 0.50 to about 0.70.

10       Further still, the formulation provides, for example ranges of C<sub>max</sub> (fasting patient) divided by C<sub>max</sub> (fed patient) from about 0.90 to about 1.10.

#### BRIEF DESCRIPTION OF THE FIGURES

15       Figure 1 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) and conducted as a Type II dissolution with a pH change to simulate gastric passage and stirring at 50 rpm.

20       Figure 2 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) and conducted as a Type III dissolution with a pH change to simulate gastric passage and stirring at 15 rpm.

25       Figure 3 shows an albuterol plasma profile of provided by ingestion of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10): solid circles mark curve of plasma profile in fed subject; open circles mark curve of plasma profile in  
30       fasted subject.

#### DETAILED DESCRIPTION

      As reported in U.S. Patent Nos. 4,994,276, 5,128,143, and 5,135,757, the disclosures of which are  
35       hereby incorporated by reference herein in their entireties, the heterodisperse excipient comprises a

5       gelling agent of both hetero- and homo-polysaccharides  
which exhibit synergism, e.g., the combination of two  
or more polysaccharide gums produce a higher viscosity  
and faster hydration than that which would be expected  
by either of the gums alone, the resultant gel being  
10       faster-forming and more rigid.

      In the present invention, it has been found that a  
sustained release excipient comprising only the gelling  
agent (heterodisperse polysaccharides, e.g., xanthan  
gum and locust bean gum, may not be sufficient to  
15       provide a suitable sustained release of an active  
medicament to provide a 12 or 24 hour formulation, when  
the formulation is exposed to a fluid in an environment  
of use, e.g. an aqueous solution or gastrointestinal  
fluid.

20       In certain embodiments, the present invention is  
related to the surprising discovery that by granulating  
the sustained release excipient with a solution or  
dispersion of a pharmacologically acceptable  
hydrophobic material prior to admixture of the  
25       sustained release excipient with the medicament and  
tableting, the medicament may provide therapeutically  
effective blood levels for extended periods of time,  
e.g., from about 12 to about 24 hours. The hydrophobic  
material is present in a range from about 0 to about  
30       90%, by weight, of the sustained release excipient and  
in a preferred embodiment, is present in a range from  
about 1 to 20 percent of the sustained release  
excipient or from about 25 to about 75 percent of the  
sustained release excipient.

35       The sustained release excipient can be granulated  
with a pharmacologically acceptable hydrophobic  
material such as, for, example, an alkylcellulose, a

5 cellulose ether, a cellulose ester. In particular, the hydrophobic material can be alkylcellulose such as carboxymethylcellulose ("CMC"), cellulose acetate phthalate ("CAP"), hydroxypropylmethylcellulose phthalate ("HPMCP") or a polyvinyl acetate polymer such  
10 as polyvinyl acetate phthalate ("PVAP").

In certain preferred embodiments of the present invention, the sustained release excipient is prepared by mixing the gelling agent and an inert diluent. The gelling agent preferably ranges, e.g., from about 10 to  
15 about 75 percent of the sustained release excipient. Thereafter, the mixture is granulated with a solution or dispersion of a hydrophobic material in an amount effective to slow the hydration of the gelling agent without disrupting the hydrophilic matrix. Next, the  
20 medicament is added, and the resultant mixture is tableted.

In other preferred embodiments of the present invention, the tablets prepared as set forth above are then coated with a hydrophobic material to a weight  
25 gain from about 1 to about 20 percent by weight. The hydrophobic material can be an alkylcellulose such as, for example, an aqueous dispersion of ethylcellulose (commercially available, for example, as Aquacoat®, available from FMC or Surelease®, available from  
30 Colorcon).

The term "heteropolysaccharide" as used in the present invention is defined as a water-soluble polysaccharide containing two or more kinds of sugar  
units, the heteropolysaccharide having a branched or  
35 helical configuration, and having excellent water-wicking properties and immense thickening properties.

An especially preferred heteropolysaccharide is

5        xanthan gum, which is a high molecular weight ( $>10^6$ )  
heteropolysaccharide. Other preferred  
heteropolysaccharides include derivatives of xanthan  
gum, such as deacylated xanthan gum, the carboxymethyl  
ether, and the propylene glycol ester.

10        The homopolysaccharide gums used in the present  
invention which are capable of cross-linking with the  
heteropolysaccharide include the galactomannans, i.e.,  
polysaccharides which are composed solely of mannose  
and galactose. Galactomannans which have higher  
15        proportions of unsubstituted mannose regions have been  
found to achieve more interaction with the  
heteropolysaccharide. Locust bean gum, which has a  
higher ratio of mannose to galactose, is especially  
preferred as compared to other galactomannans such as  
20        guar and hydroxypropyl guar.

      The controlled release properties of the  
formulations of the present invention may be optimized  
when the ratio of heteropolysaccharide gum to  
homopolysaccharide material is about 1:1, although  
25        heteropolysaccharide gum in an amount of from about 20  
to about 80 percent or more by weight of the  
heterodisperse polysaccharide material provides an  
acceptable slow release product. The combination of  
any homopolysaccharide gums known to produce a  
30        synergistic effect when exposed to aqueous solutions  
may be used in accordance with the present invention.  
It is also possible that the type of synergism which is  
present with regard to the gum combination of the  
present invention could also occur between two  
35        homogeneous or two heteropolysaccharides. Other  
acceptable gelling agents which may be used in the  
present invention include those gelling agents well-

5 known in the art. Examples include vegetable gums such  
as alginates, carrageenan, pectin, guar gum, xanthan  
gum, modified starch, hydroxypropylmethylcellulose,  
methylcellulose, and other cellulosic materials such as  
10 sodium carboxymethylcellulose and  
hydroxypropylcellulose. This list is not meant to be  
exclusive.

The combination of xanthan gum with locust bean  
gum with or without the other homopolysaccharide gums  
is an especially preferred gelling agent. The  
15 chemistry of certain of the ingredients comprising the  
excipients of the present invention such as xanthan gum  
is such that the excipients are considered to be self-  
buffering agents which are substantially insensitive to  
the solubility of the medicament and likewise  
20 insensitive to the pH changes along the length of the  
gastrointestinal tract.

The inert pharmaceutical diluent (i.e., filler) of  
the sustained release excipient preferably comprises a  
pharmaceutically acceptable saccharide, including a  
25 monosaccharide, a disaccharide, or a polyhydric  
alcohol, a pre-manufactured direct compression diluent,  
and/or mixtures of any of the foregoing. Examples of  
suitable inert pharmaceutical fillers include sucrose,  
dextrose, lactose, microcrystalline cellulose,  
30 fructose, xylitol, sorbitol, a starch, mixtures thereof  
and the like. However, it is preferred that a soluble  
pharmaceutical filler such as lactose, dextrose,  
sucrose, or mixtures thereof be used. If the mixture  
is to be manufactured without a wet granulation step,  
35 and the final product is to be tableted, it is  
preferred that all or part of the inert diluent  
comprise a pre-manufactured direct compression diluent.

5       Such direct compression diluents are widely used in the  
pharmaceutical arts, and may be obtained from a wide  
variety of commercial sources. Examples of such pre-  
manufactured direct compression excipients include  
Emcocel® (microcrystalline cellulose, N.F.), Emdex®  
10       (dextrates, N.F.), and Tab-Fine® (a number of direct-  
compression sugars including sucrose, fructose, and  
dextrose), all of which are commercially available from  
Edward Mendell Co., Inc., Patterson, New York). Other  
direct compression diluents include Anhydrous lactose  
15       (Lactose N.F., anhydrous direct tableting) from  
Sheffield Chemical, Union, N.J. 07083; Elcems® G-250  
(Powdered cellulose, N.F.) from Degussa, D-600  
Frankfurt (Main) Germany; Maltrin® (Agglomerated  
maltodextrin) from Grain Processing Corp., Muscatine,  
20       IA 52761; Neosorb 60® (Sorbitol, N.F., direct-  
compression) from Roquette Corp., 645 5th Ave., New  
York, NY 10022; Nu-Tab® (Compressible sugar, N.F.) from  
Ingredient Technology, Inc., Pennsauken, NJ 08110;  
Polyplasdane XL® (Crospovidone, N.F., cross-linked  
25       polyvinylpyrrolidone) from GAF Corp., New York, NY  
10020; Primojel® (Sodium starch glycolate, N.F.,  
carboxymethyl starch) from Generichem Corp., Little  
Falls, NJ 07424; Solka Floc® (Cellulose floc) from  
Edward Mendell Co., Carmel, NY 10512; Fast-Flo Lactose®  
30       (Lactose N.F., spray dried) from Foremost Whey  
Products, Baraboo, WI 53913 and DMV Corp., Vehgel,  
Holland; and Sta-Rx 1500® (Starch 1500) (Pregelatinized  
starch, N.F., compressible) from Colorcon, Inc., West  
Point, PA 19486. However, it is preferred that a  
35       soluble pharmaceutical filler such as lactose,  
dextrose, sucrose, or mixtures thereof be used.

In certain embodiments of the present invention,



5 the sustained release excipient comprises from about 10  
to about 99 percent by weight of a gelling agent  
comprising a heteropolysaccharide gum and a  
homopolysaccharide gum and from about 0 to about 89  
percent by weight of an inert pharmaceutical diluent.  
10 In other embodiments, the sustained release excipient  
comprises from about 10 to about 75 percent gelling  
agent, and from about 30 to about 75 percent inert  
diluent. In yet other embodiments, the sustained  
release excipient comprises from about 30 to about 75  
15 percent gelling agent and from about 15 to about 65  
percent inert diluent.

The sustained release excipient of the present  
invention may be further modified by incorporation of a  
hydrophobic material which slows the hydration of the  
20 gums without disrupting the hydrophilic matrix. This  
is accomplished in preferred embodiments of the present  
invention by granulating the sustained release  
excipient with the solution or dispersion of a  
hydrophobic material prior to the incorporation of the  
25 medicament. The hydrophobic material may be selected  
from an alkylcellulose such as ethylcellulose such as  
carboxymethyl-cellulose ("CMC"), other hydrophobic  
cellulosic materials, acrylic and/or methacrylic ester  
polymers, copolymers of acrylic and methacrylic esters,  
30 zein, waxes, other hydrophobic cellulosic materials,  
cellulose acetate phthalate ("CAP"),  
hydroxypropylmethylcellulose phthalate ("HPMCP") or a  
polyvinyl acetate polymer such as polyvinyl acetate  
phthalate ("PVAP"), hydrogenated vegetable oils, and  
35 any other pharmaceutically acceptable hydrophobic  
material known to those skilled in the art. The amount  
of hydrophobic material incorporated into the sustained

5        release excipient is that which is effective to slow  
the hydration of the gums without disrupting the  
hydrophilic matrix formed upon exposure to an  
environmental fluid.

10        In certain preferred embodiments of the present  
invention, the hydrophobic material is included in the  
sustained release excipient in an amount from about 1  
to about 20 percent by weight. The solvent for the  
hydrophobic material may be an aqueous or organic  
solvent, or mixtures thereof.

15        Examples of commercially available alkylcelluloses  
are Aquacoat® (aqueous dispersion of ethylcellulose  
available from FMC), Surelease® (aqueous dispersion of  
ethylcellulose available from Colorcon). Examples of  
commercially available acrylic polymers suitable for  
20        use as the hydrophobic material include Eudragit® RS  
and RL (copolymers of acrylic and methacrylic acid  
esters having a low content (e.g., 1:20 or 1:40) of  
quaternary ammonium compounds).

25        Once the sustained release excipient of the  
present invention has been prepared, it is then  
possible to blend the same with the medicament, e.g.,  
in a high shear mixer. In one embodiment, the  
formulation is prepared by dry blending the components,  
e.g., a heteropolysaccharide, a homopolysaccharide, an  
30        inert filler, and a hydrophobic material, optionally  
followed by the addition of a suitable amount of water,  
with continued blending, followed by dry granulation in  
a fluid bed dryer and then milling of the resulting  
granulation product.

35        A wide variety of therapeutically active agents  
can be used in conjunction with the present invention.  
The therapeutically active agents (e.g., pharmaceutical

5 agents) which may be used in the compositions of the  
present invention include drugs ranging in solubility  
from water soluble to water insoluble. Examples of  
such therapeutically active agents include  
antihistamines (e.g., dimenhydrinate, diphenhydramine,  
10 chlorpheniramine and dexchlorpheniramine maleate),  
analgesics (e.g., aspirin, codeine, morphine,  
dihydromorphone, oxycodone, etc.), non-steroidal anti-  
inflammatory agents (e.g., naproxyn, diclofenac,  
indomethacin, ibuprofen, sulindac), anti-emetics (e.g.,  
15 metoclopramide), anti-epileptics (e.g., phenytoin,  
meprobamate and nitrazepam), vasodilators (e.g.,  
nifedipine, papaverine, diltiazem and nicardirine),  
anti-tussive agents and expectorants (e.g., codeine  
phosphate), anti-asthmatics (e.g. theophylline),  
20 antacids, anti-spasmodics (e.g. atropine, scopolamine),  
antidiabetics (e.g., insulin), diuretics (e.g.,  
ethacrynic acid, bendrofluazide), anti-hypotensives  
(e.g., propranolol, clonidine), antihypertensives  
(e.g., clonidine, methyldopa), bronchodilators (e.g.,  
25 albuterol), steroids (e.g., hydrocortisone,  
triamcinolone, prednisone), antibiotics (e.g.,  
tetracycline), antihemorrhoidals, hypnotics,  
psychotropics, antidiarrheals, mucolytics, sedatives,  
decongestants, laxatives, vitamins, stimulants  
30 (including appetite suppressants such as  
phenylpropanolamine). The above list is not meant to  
be exclusive.

In a preferred embodiment, the therapeutically  
active agents are sympathomimetics such as, dobutamine  
35 hydrochloride, dopamine hydrochloride, ephedrine  
sulfate, epinephrine, fenfluramine hydrochloride,  
isoetharine, isoproterenol, mephentermine sulfate,

5       metaproterenol sulfate, metaraminol bitartrate,  
methoxamine hydrochloride, norepinephrine bitartrate,  
phenylephrine hydrochloride, phenylpropanolamine  
hydrochloride, pseudoephedrine, ritodrine  
hydrochloride, terbutaline sulfate, tetrahydrozoline  
10       hydrochloride, triprolidine and pseudoephedrine,  
xylometazoline hydrochloride, isoproterenol and  
dobutamine as well as beta2 selective adrenergic  
agonists, including, for example, terbutaline,  
albuterol, isoetharine, pirbuterol and bitolterol  
15       (GOODMAN AND GILMAN's, THE PHARMACOLOGICAL BASIS OF  
THERAPEUTICS, Eighth Edition, the disclosure of which  
is incorporated herein by reference in its entirety).

Generally any flavoring or food additive such as  
those described in Chemicals Used in Food Processing,  
20       pub 1274 by the National Academy of Sciences, pages 63-  
258, incorporated herein in its entirety, may be used.  
Generally, the final product may include from about  
0.1% to about 5% by weight flavorant.

The tablets of the present invention may also  
25       contain effective amounts of coloring agents, (e.g.,  
titanium dioxide, F.D. & C. and D. & C. dyes; see the  
Kirk-Othmer Encyclopedia of Chemical Technology, Vol.  
5, pp. 857-884, hereby incorporated by reference in its  
entirety), stabilizers, binders, odor controlling  
30       agents, and preservatives.

Alternatively, the inventive formulation can be  
utilized in other applications wherein it is not  
compressed. For example, the granulate can be admixed  
with an active ingredient and the mixture then filled  
35       into capsules. The granulate can further be molded  
into shapes other than those typically associated with  
tablets. For example, the granulate together with

5 active ingredient can be molded to "fit" into a particular area in an environment of use (e.g., an implant). All such uses would be contemplated by those skilled in the art and are deemed to be encompassed within the scope of the appended claims.

10 A hydrophobic material (e.g., a hydrophobic polymer) may be dissolved in an organic solvent or dispersed in an aqueous solution. Thereafter, the hydrophobic material may be used to coat the granulate of medicament/sustained release excipient. The  
15 granulate may be coated with the hydrophobic coating to a weight gain of, e.g., from about 1 to about 20 percent, and preferably from about 5 to about 10 percent. The granulation is then preferably dried. Thereafter, the granulate may be further formulated  
20 into an appropriate oral dosage form, for example, by compression of the resulting granulate into appropriately sized tablets, by filling gelatin capsules with an appropriate amount of the granulate (with or without compression of the granulate), as well  
25 as use in the manufacture of other oral dosage forms known to those skilled in the art. This embodiment may be particularly beneficial to reduce the amount of drug released during the initial phases of dissolution when the formulation is exposed to fluid in an environment  
30 of use, e.g., in vitro dissolution or in the gastrointestinal tract.

An effective amount of any generally accepted pharmaceutical lubricant, including the calcium or magnesium soaps may be added to the above-mentioned  
35 ingredients of the excipient be added at the time the medicament is added, or in any event prior to compression into a said dosage form. An example of a

5        suitable lubricant is magnesium stearate in an amount of about 0.5 to about 3% by weight of the solid dosage form. An especially preferred lubricant is sodium stearyl fumarate, NF, commercially available under the trade name Pruv® from the Edward Mendell Co., Inc.

10        The sustained release excipients of the present invention have uniform packing characteristics over a range of different particle size distributions and are capable of processing into the final dosage form (e.g., tablets) using either direct compression, following  
15        addition of drug and lubricant powder, or conventional wet granulation.

      The properties and characteristics of a specific excipient system prepared according to the present invention is dependent in part on the individual  
20        characteristics of the homo and hetero polysaccharide constituents, in terms of polymer solubility, glass transition temperatures etc., as well as on the synergism both between different homo- and heteropolysaccharides and between the homo and  
25        heteropolysaccharides and the inert saccharide constituent(s) in modifying dissolution fluid-excipient interactions.

      The combination of the gelling agent (i.e., a mixture of xanthan gum and locust beam gum) with the  
30        inert diluent provides a ready-to-use product in which a formulator need only blend the desired active medicament and an optional lubricant with the excipient and then compress the mixture to form slow release tablets. The excipient may comprise a physical admix  
35        of the gums along with a soluble excipient such as compressible sucrose, lactose or dextrose, although it is preferred to granulate or agglomerate the gums with

5 plain (i.e., crystalline) sucrose, lactose, dextrose,  
etc., to form an excipient. The granulate form has  
certain advantages including the fact that it can be  
optimized for flow and compressibility; it can be  
tableted, formulated in a capsule, extruded and  
10 spheronized with an active medicament to form pellets,  
etc.

The pharmaceutical excipients prepared in  
accordance with the present invention may be prepared  
according to any agglomeration technique to yield an  
15 acceptable excipient product. In dry granulation  
techniques, the excipients, i.e., the desired amounts  
of the heteropolysaccharide gum, the homopolysaccharide  
gum, and the inert diluent are mixed with an active  
medicament and the mixture is then formed into tablets  
20 and the like by compression, without the addition of  
water or other solvent.

In wet granulation techniques, the desired amounts  
of the heteropolysaccharide gum, the homopolysaccharide  
gum, and the inert diluent are mixed together and  
25 thereafter a moistening agent such as water, propylene  
glycol, glycerol, alcohol or the like is added to  
prepare a moistened mass. Next, the moistened mass is  
dried. The dried mass is then milled with conventional  
equipment into granules. Therefore, the excipient  
30 product is ready to use.

The sustained release excipient is free-flowing  
and directly compressible. Accordingly, the excipient  
may be mixed in the desired proportion with a  
therapeutically active medicament and optional  
35 lubricant (dry granulation). Alternatively, all or  
part of the excipient may be subjected to a wet  
granulation with the active ingredient and thereafter

5       tableted. When the final product to be manufactured is  
tablets, the complete mixture, in an amount sufficient  
to make a uniform batch of tablets, is then subjected  
to tableting in a conventional production scale  
tableting machine at normal compression pressure, i.e.  
10       about 2000-1600 lbs/sq in. However, the mixture should  
not be compressed to such a degree that there is  
subsequent difficulty in its hydration when exposed to  
gastric fluid.

15       One of the limitations of direct compression as a  
method of tablet manufacture is the size of the tablet.  
If the amount of active (drug) is high, a  
pharmaceutical formulator may choose to wet granulate  
the active medicament with other excipients to attain a  
more compact tablet. Usually the amount of  
20       filler/binder or excipients needed in wet granulation  
is less than that in direct compression since the  
process of wet granulation contributes to some extent  
toward the desired physical properties of a tablet.

25       The average tablet size for round tablets is  
preferably about 300 mg to 750 mg and for capsule-  
shaped tablets about 750 mg to 1000 mg.

30       The average particle size of the granulated  
excipient of the present invention ranges from about 50  
microns to about 400 microns and preferably from about  
185 microns to about 265 microns. The particle size of  
the granulation is not narrowly critical, the important  
parameter being that the average particle size of the  
granules, must permit the formation of a directly  
compressible excipient which forms pharmaceutically  
35       acceptable tablets. The desired tap and bulk densities  
of the granulation of the present invention are  
normally between from about 0.3 to about 0.8 g/ml, with



5 an average density of from about 0.5 to about 0.7 g/ml.  
For best results, the tablets formed from the  
granulations of the present invention are from about 6  
to about 8 kg hardness. The average flow of the  
granulations prepared in accordance with the present  
10 invention are from about 25 to about 40 g/sec. Tablets  
compacted using an instrumented rotary tablet machine  
have been found to possess strength profiles which are  
largely independent of the inert saccharide component.  
Scanning electron photomicrographs of largely tablet  
15 surfaces have provided qualitative evidence of  
extensive plastic deformation on compaction, both at  
the tablet surface and across the fracture surface, and  
also show evidence of surface pores through which  
initial solvent ingress and solution egress may occur.

20 In certain embodiments of the invention, the  
tablet is coated with a sufficient amount of a  
hydrophobic material, such as, e.g., a hydrophobic  
polymer, to render the formulation capable of providing  
a release of the medicament such that a 12 or 24 hour  
25 formulation is obtained. The hydrophobic material  
included in the tablet coating may be the same or  
different material as compared to the hydrophobic  
material which is optionally granulated with the  
sustained release excipient.

30 In other embodiments of the present invention, the  
tablet coating may comprise an enteric coating material  
in addition to or instead of the hydrophobic coating.  
Examples of suitable enteric polymers include cellulose  
acetate phthalate, hydroxypropylmethylcellulose  
35 phthalate, polyvinylacetate phthalate, methacrylic acid  
copolymer, shellac, hydroxypropylmethylcellulose  
succinate, cellulose acetate trimellitate, and mixtures

5 of any of the foregoing. An example of a suitable commercially available enteric material is available under the trade name Eudragit™ L 100-555.

10 In further embodiments, the dosage form may be a coating with a hydrophilic coating in addition to or instead of the above-mentioned coatings. An example of a suitable material which may be used for such a hydrophilic coating is hydroxypropylmethylcellulose (e.g., Opadry®, commercially available from Colorcon, West Point, Pennsylvania).

15 The coatings may be applied in any pharmaceutically acceptable manner known to those skilled in the art. For example, in one embodiment, the coating is applied via a fluidized bed or in a coating pan. For example, the coated tablets may be dried, e.g., at about 60-70°C for about 3-4 hours in a coating pan. The solvent for the hydrophobic material or enteric coating may be organic, aqueous, or a mixture of an organic and an aqueous solvent. The organic solvents may be, e.g., isopropyl alcohol, ethanol, and the like, with or without water.

25 In additional embodiments of the present invention, a support platform is applied to the tablets manufactured in accordance with the present invention. Suitable support platforms are well known to those skilled in the art. An example of suitable support platforms is set forth, e.g., in U.S. Patent No. 30 4,839,177, hereby incorporated by reference herein in its entirety. In that patent, the support platform partially coats the tablet, and consists of a polymeric material insoluble in aqueous liquids. The support platform may, for example, be designed to maintain its impermeability characteristics during the transfer of 35

5 the therapeutically active medicament. The support platform may be applied to the tablets, e.g., via compression coating onto part of the tablet surface, by spray coating the polymeric materials comprising the support platform onto all or part of the tablet surface, or by immersing the tablets in a solution of the hydrophobic materials.

10 The support platform may have a thickness of, e.g., about 2 mm if applied by compression, and about 10  $\mu$  if applied via spray-coating or immersion-coating. Generally, in embodiments of the invention wherein a hydrophobic material or enteric coating is applied to the tablets, the tablets are coated to a weight gain from about 1 to about 20%, and in certain embodiments preferably from about 5% to about 10%.

20 Materials useful in the hydrophobic coatings and support platforms of the present invention include derivatives of acrylic acid (such as esters of acrylic acid, methacrylic acid, and copolymers thereof) celluloses and derivatives thereof (such as ethylcellulose), polyvinylalcohols, and the like.

25 In certain embodiments of the present invention, the tablet core includes an additional dose of the medicament included in either the hydrophobic or enteric coating, or in an additional overcoating coated on the outer surface of the tablet core (without the hydrophobic or enteric coating) or as a second coating layer coated on the surface of the base coating comprising the hydrophobic or enteric coating material. This may be desired when, for example, a loading dose of a therapeutically active agent is needed to provide therapeutically effective blood levels of the active agent when the formulation is first exposed to gastric

30

35

5 fluid. The loading dose of medicament included in the coating layer may be, e.g., from about 10% to about 40% of the total amount of medicament included in the formulation.

10 Albuterol Controlled Release Formulation

In a more preferred embodiment, the therapeutically active agent is albuterol, or salts or derivatives thereof (e.g., albuterol sulfate). Albuterol sulfate is a beta2 - selective adrenergic agonist and is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease. Patient compliance and evenly maintained blood levels of the active drug are important for achieving good control of the symptoms of bronchospasm in such patients. The half-life of albuterol sulfate in the human body is only about 5 hours. Thus, a controlled release form for the sustained delivery of albuterol provides improved patient compliance by reducing the number of doses per day and also provides more consistent blood levels of albuterol for patients in need of such treatment.

The albuterol controlled release formulation is composed of synergistic heterodisperse polysaccharides together with a saccharide component. The synergism between the homo- and hetero-polysaccharide components enables the manipulation of different rate controlling mechanisms. In order to achieve appropriate drug release, the saccharides were optimized based upon the magnitude of interactions and the ratio of one saccharide to another.

5        Preparation

          The albuterol containing formulation according to the invention is prepared, for example, by dry blending the components, e.g., a heteropolysaccharide, a homopolysaccharide, an inert filler, and a hydrophobic material, followed by the addition of a suitable amount of water, with continued blending, followed by dry granulation in a fluid bed dryer and then milling of the resulting granulation product. Albuterol sulfate, in an amount ranging from, e.g., about 2 through about 50% by weight of the total formulation, or preferably from about 1 through about 10% by weight or more preferably from about 1 through about 6% by weight of the total formulation, is then compounded with the granulation product and formed into pills, caplets or capsules. Whatever the formulation, it is preferred that such pills, caplets or capsules each contain an effective therapeutic amount of albuterol or a derivative or salt thereof. Simply by way of example, the pills, caplets or capsules can contain an amount of albuterol sulfate equivalent to about 4 to about 16 mg of albuterol free base per dosage unit of the free base. More preferably, the pills, caplets or capsules can contain an amount of albuterol sulfate equivalent to about 8 to about 12 mg of the free base. Simply by way of comparison, 9.6 mg of albuterol sulfate is equivalent to 8 mg of free base. Effective amounts of other pharmaceutically acceptable albuterol derivatives or salts thereof may be used, with the amounts adjusted in proportion to the weight ranges provided for albuterol free base.

5        Dissolution Testing

          The test formulations were evaluated under a variety of dissolution conditions to determine the effects of pH, media, agitation and apparatus. Dissolution tests were performed using a USP Type III (VanKel Bio-Dis II) apparatus. Effects of pH, agitation, polarity, enzymes and bile salts were evaluated.

10

Bioavailability Study

15        A study was conducted to evaluate the bioavailability of a test formulation of albuterol sulfate using a randomized, balanced, open label, single dose, crossover design. The study was performed using 12 healthy male and female volunteers between the ages of 18 and 35. Blood samples were removed at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 15 and 25 hours. Except for the "fed" treatment in which the subjects received a standard high fat breakfast, no food was allowed until a standard lunch was served four hours after the dose was administered. The data from each time point were used to derive pharmacokinetic parameters: area under plasma concentration-time curve ("AUC") such as AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, mean peak plasma concentration ("C<sub>max</sub>") and time to mean peak plasma concentration ("T<sub>max</sub>") which data confirmed that the formulation according to the invention provided controlled release of albuterol sulfate.

20

25

30

          The invention is further described in the following examples, based upon the above described methods, which are in no way intended to limit the scope of the invention.

35

5

EXAMPLES 1-2Preparation of Controlled Release Formulations with  
Carboxymethylcellulose and Dissolution Tests Thereon

10

15

20

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent in a high-speed mixer/granulator for 2 minutes. While running choppers/impellers, the water was added and the mixture was granulated for another 2 minutes. The granulation was then dried in a fluid bed dryer to a loss on drying weight ("LOD") of between 4 and 7%. The granulation was then milled using 20 mesh screens. The ingredients of the sustained release excipients used for Examples 1-2 are set forth in Table 1 below:

TABLE 1

25

The hydrophobic polymer is carboxymethylcellulose ("CMC").

30

Component	Example 1	Example 2
1. Xanthan gum	10%	10%
2. Locust bean gum	10	10
3. CMC	10	30
4. Dextrose	70	50
5. Water	23*	23*

35

\* Removed during processing.

40

Next, the sustained release excipient prepared as detailed above is dry blended with a desired amount of medicament (in the following examples the medicament is albuterol sulfate), in a V-blender for 10 minutes. A suitable amount of tableting lubricant Pruv® (sodium stearyl fumarate, NF, commercially available from the

30

Edward Mendell Co., Inc.) for the following examples is added and the mixture is blended for another 5 minutes. This final mixture is compressed into tablets, each tablet containing 2.9% (Ex. 1) or 4.7% (Ex. 2) by weight, respectively, of albuterol sulfate. The tablets produced by Examples 1 and 2 weighed 334.6 mg and 204.7 mg, respectively. The proportions of the tablets of Examples 1 and 2 are set forth in Table 2 below.

TABLE 2

Component	Example 1	Example 2
1. SRE*	95.6%	93.8%
2. Albuterol sulfate	2.9	4.7
3. Sodium stearyl fumarate	1.5	1.5

\*Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 1 and 2. The dissolution tests were conducted in an automated USP dissolution apparatus (Paddle Type II, pH 7.5 buffer, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours.

TABLE 3

Time (hrs)	Example 1	Example 2
0 (% release)	0.0	0.0
2	28.2	30.7
4	41.5	49.5
6	54.5	67.2
8	64.3	79.8
10	71.0	91.2
12	78.7	96.5
Tablet wt(mg)	334.6	204.7
Diameter (in)	3/8	3/8
Hardness (Kp)	6.5	2.6



5 The tablet of Example 1, with a higher percentage of sustained release excipient, provided the most prolonged release in the dissolution test.

10 EXAMPLES 3-4  
Preparation of Controlled Release  
Formulations with Cellulose Acetate  
Phthalate and Dissolution Tests Thereon

15 The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1-2, *supra*, but with cellulose acetate phthalate ("CAP") as the hydrophobic polymer, as  
20 detailed by Table 4, below, for Examples 3 and 4.

TABLE 4

Component	Example 3	Example 4
1. Xanthan gum	15%	15%
2. Locust bean gum	15	15
3. CAP	10	30
4. Dextrose	60	40
5. Water	10*	17*

30 \* Removed during processing.

35 Next, the sustained release excipient prepared as detailed above was dry blended with a desired amount of albuterol sulfate, as described for Examples 1-2, *supra*. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 3 and 4 weighed 334.6 mg. The proportions of the tablets of Examples 3 and 4 are set forth in Table 5 below:

5

TABLE 5

Component	Example 3	Examples 4
1. SRE*	95.6%	95.6%
2. Albuterol sulfate	2.9	2.9
3. Sodium stearyl fumarate	1.5	1.5

10

\*Sustained release excipient.

15

20

Dissolution tests were then carried out on the tablets of Examples 3 and 4. The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, in the stomach (acid buffer with a pH of 1.5 for time: 0 through 1 hour) and in the intestines (alkaline buffer with a pH of 7.5 for time: 1 through 12 hours) (Paddle Type II, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours, in Table 6 below.

25

TABLE 6

Time (hrs)	Example 3	Example 4
0 (% release)	0.0	0.0
1	36.0	36.2
2	50.2	49.4
4	65.1	61.4
6	73.5	70.7
8	83.1	77.0
10	86.3	81.6
12	91.0	86.1
Tablet wt(mg)	334.6	334.6
Diameter (in)	3/8	3/8
Hardness (Kp)	5.8	5.8

35

40

The tablet tested in Example 4 provided the most

5 prolonged release in the dissolution test.

EXAMPLES 5-6

Preparation of Controlled Release Formulations with  
10 Polyvinyl Acetate Phthalate and Dissolution Tests  
Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable  
15 hydrophobic polymer and an inert diluent as described for Examples 1-2, *supra*, but with polyvinyl acetate phthalate ("PVAP") as the hydrophobic polymer, as detailed by Table 7, below, for Examples 5 and 6.

20 TABLE 7

<u>Component</u>	<u>Example 5</u>	<u>Example 6</u>
1. Xanthan gum	15%	15%
2. Locust bean gum	15	15
3. PVAP	10	30
25 4. Dextrose	60	40
5. Water	18*	23*

\* Removed during processing.

Next, the sustained release excipient prepared as  
30 detailed above was dry blended with a desired amount of albuterol sulfate, as described for Examples 1-2, *supra*. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 5  
35 and 6 weighed 334.6 mg, respectively. The proportions of the tablets of Examples 5 and 6 are set forth in Table 8 below:

5

TABLE 8

Component	Example 5	Example 6
1. SRE*	95.6%	95.6%
2. Albuterol sulfate	2.9	2.9
3. Sodium stearyl fumarate	1.5	1.5

10

\*Sustained release excipient.

15

Dissolution tests were then carried out on the tablets of Examples 5 and 6. The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, in the stomach (acid buffer with a pH of 1.5 for time: 0 through 1 hour) and in the intestines (alkaline buffer with a pH of 7.5 for time: 1 through 12 hours) (Paddle Type II, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours, in Table 9 below.

20

TABLE 9

Time (hrs)	Example 5	Example 6
0 (% release)	0.0	0.0
1	36.4	36.5
2	51.3	47.4
4	66.2	57.6
6	71.8	66.0
8	79.9	70.4
10	84.2	77.2
12	86.4	77.7

30

35

Tablet wt(mg)	334.6	334.6
Diameter (in)	3/8	3/8
Hardness (Kp)	5.9	8.6

40

The tablet tested in Example 6 provided the most prolonged release in the dissolution test.

5

EXAMPLES 7-8

Preparation of Controlled Release Formulations  
with Hydroxypropylmethylcellulose  
10 Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable  
15 hydrophobic polymer and an inert diluent as described for Examples 1-2, *supra*, but with hydroxypropylmethylcellulose phthalate ("HPMCP") as the hydrophobic polymer, as detailed by Table 10, below, for Examples 7 and 8.

20

TABLE 10

Component	Example 7	Example 8
1. Xanthan gum	15%	15%
2. Locust bean gum	15	15
3. HPMCP	10	30
25 4. Dextrose	60	40
5. Water	13*	18*

\* Removed during processing.

30

As for the previous examples, the sustained release excipient was prepared as detailed above and then dry blended with a desired amount of albuterol sulfate, as described for Examples 1-2, *supra*. This final mixture was then compressed into tablets, each  
35 tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 7 and 8 weighed 334.6 mg, respectively. The proportions of the tablets of Examples 7 and 8 are set forth in Table 11 below:

40

TABLE 11

Component	Example 7	Example 8
-----------	-----------	-----------

36

- 5           1. SRE\*                           95.6%                   95.6%  
           2. Albuterol sulfate           2.9                   2.9  
           3. Sodium stearyl fumarate   1.5                   1.5

10                   \*Sustained release excipient.

10                   The dissolution tests were conducted in an auto-  
                     mated USP dissolution apparatus in such a way as to  
                     model passage through the gastrointestinal tract, as  
                     described supra for, e.g., Examples 5-6. The results  
                     are set forth as percent release as a function of time,  
                     in hours, in Table 12 below.

TABLE 12

	Time (hrs)	Example 7	Example 8
20	0 (% release)	0.0	0.0
	1	33.7	32.7
	2	48.2	42.8
	4	63.9	60.3
	6	74.8	71.2
25	8	79.6	74.6
	10	85.6	82.3
	12	87.0	87.2
<hr/>			
	Tablet wt(mg)	334.6	334.6
30	Diameter (in)	3/8	3/8
	Hardness (Kp)	6.5	8.3

35                   The data of Table 12 indicates that both Examples  
                     7 and 8 provided effective prolongation of albuterol  
                     release in the dissolution test.

## EXAMPLES 9-12

40                   Preparation of Controlled Release Formulations  
                     with Ethylcellulose Coating and Dissolution Tests  
                     Thereon

5

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum and an inert diluent as described for Examples 1-2, *supra*, but with no hydrophobic polymer, and with an extra 2 minutes of granulation after the addition of the components (for 4 total minutes of post-addition granulation). Ethylcellulose aqueous dispersion was substituted for water in the above methods. The components of the excipient for Examples 9-12 are detailed by Table 13, below.

10

15

TABLE 13

	<u>Component</u>	<u>Excipient for Examples 9-12</u>
20	1. Xanthan gum	12%
	2. Locust bean gum	18
	3. Dextrose	65
	4. EAD*	5*

25

\* EAD is an ethylcellulose aqueous dispersion containing approximately 25% by weight of solids. The amount added to the formulation (i.e., 5%) is solids only. Available commercially as, e.g., Surelease®, from Colorcon.

30

35

The xanthan gum and locust bean gum was dry blended in a V-blender for 10 minutes, the dextrose was added and the mixture blended for another 5 minutes. The EAD was then added, followed by an additional 5 minutes of blending. The resulting granulation was then compressed into tablets with sodium stearyl fumarate, as a tableting lubricant. The tablets were then coated with additional ethylcellulose aqueous

5 dispersion. To accomplish this, ethylcellulose  
(Surelease®, 400 g) was mixed with water (100 g) to  
form an aqueous suspension. Thereafter, the tablets  
were coated in a Keith Machinery coating pan (diameter  
350 mm; pan speed 20 rpm; spray-gun nozzle 0.8 mm;  
10 tablets bed temperature 40°-50°C; charge per batch 1 kg;  
dry air - Conair Prostyle 1250, 60°-70°C). The tablets  
were coated to a weight gain of about 5%.

The tablets weighed 181.4 mg, respectively. The  
proportions of the tablets are set forth in Table 14  
15 below:

TABLE 14

20	<u>Component</u>	<u>Percent</u>
	1. SRE*	8.2%
	2. Albuterol sulfate	5.3
	3. Polyvinyl acetate phthalate	5.0
25	4. Sodium stearyl fumarate	1.5
	*Sustained release excipient.	

The dissolution tests were conducted in an auto-  
mated USP dissolution apparatus in such a way as to  
model passage through the gastrointestinal tract, as  
described *supra* for, e.g., Examples 5-6. The results  
30 are set forth as percent release as a function of time,  
in hours, in Table 15, below. The columns are  
identified as "Uncoated" (Ex. 9) 2% (Ex. 10), 3% (Ex.  
11) and 4% (Ex. 12) coating by weight.



TABLE 15

	Ex. 9	Ex. 10	Ex. 11	Ex. 12
<u>Time (hrs)</u>	<u>Uncoated</u>	<u>2%</u>	<u>3%</u>	<u>4% (coat %</u>
<u>W/W)</u>				
0 (% release)	0.0	0.0	0.0	0.0
1	41.7	11.2	0.0	0.0
2	56.7	21.9	2.3	0.0
4	73.0	41.2	16.2	4.6
6	82.5	60.3	37.1	21.3
8	87.9	74.9	54.5	40.3
10	91.0	82.5	65.2	54.0
12	93.9	88.5	84.1	67.5

Tablet wt (mg)	181.4
Diameter (in)	3/8
Hardness (Kp)	7.9

The above table clearly indicates that a prolongation of release is obtained that is proportional to the percent of hydrophobic coating, by weight.

In order to determine the differences, if any, in dissolution kinetics between a fed state and a fasting state for the series of coated tablets as tested above in Examples 9-12, the same tablets were tested, in vitro, for dissolution rates in a solution containing 30% peanut oil ("fed") to model a gastrointestinal tract with a typical dietary fat load. The control determined the dissolution rates in a solution lacking the fat load ("fasted"). The pH - time protocol (ranging from acid to alkaline to model digestive processes) is set forth below in Table 16, below.

TABLE 16  
Fed/Fast Dissolution Protocol

	"Fasted"	"Fed"
Apparatus:	Type III	Type III
Media:	0 - 1 hr pH 1.5	30% peanut oil
	1 - 2 hr pH 3.5	
	2 - 4 hr pH 5.5	

5                      4 - 12 hr   pH 7.5

Agitation:	15 cpm	15 cpm
Volume:	250 mL	250 mL

10 TABLE 17  
Fed/Fast Dissolution Results

	<u>Time (hrs)</u>	<u>"Fasted"</u> Uncoated	<u>"Fasted"</u> 2%	<u>"Fed"</u> Uncoated	<u>"Fed"</u> 2%
15	0 (% release)	0.0	0.0	0.0	0.0
	1	48.8	15.5	28.8	18.4
	2	68.5	28.8	49.8	39.9
	4	87.2	49.5	91.9	78.9
	6	96.1	65.9	100.0	97.3
	8	100.0	80.7	100.0	100.0
20	12	100.0	100.0	100.0	100.0

As can be appreciated from table 17, the dissolution rates (in vitro) in the presence of 30% peanut oil ("Fed") are not significantly different from the dissolution rates in the absence of the 30% peanut oil ("Fast"), thus demonstrating both the improved control of release rate provided by the 2% ethylcellulose coating and the freedom from significant "Fed/Fast" effects provided by the formulations of the present invention.

5

### RESULTS AND DISCUSSION

Figures 1 and 2 show in vitro dissolution profiles for the product formulated according to Table 14 and Table 15 (Example 10) i.e., the formulation of Table 14 with a 2% ethylcellulose coating. The mean in vivo plasma profile for the test product is provided in Figure 3. Figure 1 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) as described above. The dissolution profile of Figure 1 was conducted as a Type II dissolution with a pH change to simulate gastric and enteric passage and stirring at 50 rpm (acid buffer with a pH of 1.5 for time: 0 through 1 hour followed by alkaline buffer with a pH of 7.5 for time: 1 through 12 hours). Figure 2 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 as described above and conducted as a Type III dissolution with a pH change to simulate gastric and enteric passage (pH profile as described by Table 16 above) and stirring at 15 rpm. Figure 3 shows an albuterol plasma profile of provided by ingestion of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10): solid circles mark curve of plasma profile in fed subject; open circles mark curve of plasma profile in fasted subjects.

Analysis of the pharmacokinetic parameters  $C_{max}$ ,  $T_{max}$ , and  $AUC_{\infty}$  (Table 18) confirms that the tested formulation is an ideal candidate for a 12 hour albuterol formulation. Furthermore, a comparison of the test product in the fed and fasted states show that

35

5 the test product is not significantly affected by food.  
A delay of gastric emptying, which is expected in the  
fed state, accounts for the extended time required to  
reach the maximum plasma concentration.

10 **Table 18: Albuterol Pharmacokinetics**

Parameter		TIMERx fasted	TIMERx fed
Cmax	mean	10.5	10.6
	%CV	39.0	31.0
Tmax	mean	4.5	7.0
	%CV	29.0	23.0
AUCInf	mean	113.4	128.1
	%CV	30.0	20.0

Ratios	Cmax	Tma	AUC Inf
TIMERx fasted: TIMERx fed	0.98	0.64	0.89
TIMERx fed: TIMERx fasted	1.02	1.57	1.13

Confidence Limits	Cmax LL	Cmax UL	AUCInf LL	AUCInf UL
TIMERx fed vs TIMERx fasted	89	124	102	133

Table 19

Parameter	TIMERx-fasted	TIMERx-fed
AUC <sub>∞</sub>	57.3-156.2	75.6-161.1
C <sub>max</sub>	4.6-18.4	6.0-15.9
T <sub>max</sub>	3.0-6.0	3.0-8.0
Parameter	TIMERx-fed	
AUC <sub>∞</sub>	89.9-149.2	
C <sub>max</sub>	7.0-11.9	
T <sub>max</sub>	3.0-10.0	

### CONCLUSION

From the results provided in above examples, it can be seen that the formulations according to the invention provide a controlled release of an active medicament such as albuterol sulfate without any significant differences induced by a "fed/fast" effect due to the presence of food in the gastrointestinal tract. Accordingly, the results provide that the tablets produced according to the invention are suitable for delivering medicaments as an oral solid dosage form over a 24-hour oral period of time.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the claims. Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

5        What is claimed is:

1. A controlled release solid dosage form for oral administration of a therapeutically active medicament to a patient in need thereof, comprising:

10        a pharmaceutically effective amount of a medicament to be administered to a patient in need of said medicament;

15        a sustained release excipient comprising a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of reciprocally cross-linking when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1; an inert pharmaceutical diluent selected from the group consisting of a pharmaceutically acceptable  
20        saccharide, polyhydric alcohol, a pre-manufactured direct compression diluent, and mixtures of any of the foregoing, the ratio of said inert diluent to said gelling agent being from about 1:8 to about 8:1, said dosage form providing a sustained release of said  
25        medicament when exposed to an environmental fluid and a pharmaceutically acceptable hydrophobic material.

30        2. The controlled release solid dosage form according claim 2 wherein said diluent is a saccharide selected from the group consisting of sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, a starch, and mixtures thereof.

35

5           3. The controlled release solid dosage form according claim 1, wherein said heteropolysaccharide gum comprises xanthan gum and said homopolysaccharide gum comprises locust bean gum.

10           4. The controlled release solid dosage form according claim 2, wherein said xanthan gum and said locust bean gum are present in about a 1:1 ratio, respectively, by weight.

15           5. The controlled release solid dosage form according to claim 1, wherein said hydrophobic material is selected from the group consisting of a cellulose ether, a cellulose ester and an alkylcellulose.

20           6. The controlled release solid dosage form according claim 1, wherein said hydrophobic material is selected from the group consisting of ethylcellulose, carboxymethylcellulose, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate and a polyvinyl  
25 acetate polymer.

            7. The controlled release solid dosage form according claim 1, wherein said hydrophobic material is present in an amount ranging from about 1 through about  
30 90%, by weight, of the solid dosage form.

            8. The controlled release solid dosage form according claim 1, wherein said hydrophobic material is present in an amount ranging from about 25% through  
35 about 50%, by weight, of the solid dosage form.

5           9. The controlled release solid dosage form according to claim 1 wherein said medicament is a pharmaceutically effective amount of albuterol or a salt or derivative thereof.

10           10. The controlled release solid dosage form according to claim 1 which is a tablet.

          11. The controlled release solid dosage form according to claim 1 which is in granular form.

15           12. The controlled release solid dosage form according to claim 11, which comprises a gelatin capsule containing a sufficient amount of said granules to provide an effective dose of said therapeutically active medicament.

          13. The controlled release solid dosage form according to claim 9, wherein said hydrophobic material is selected from the group consisting of  
25    carboxymethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate, ethylcellulose, a copolymer of acrylic and methacrylic and esters, waxes, shellac, zein, and mixtures of any of the fore-  
30    going, prior to incorporation of said medicament, said hydrophobic material being included in said dosage form in an amount effective to slow the hydration of said gelling agent when exposed to an environmental fluid.

35           14. The controlled release solid dosage form according to claim 12 which is a tablet, at least part of a surface of said tablet being coated with a



5 hydrophobic material to a weight gain from about 1 to  
about 20 percent, by weight.

15 15. The controlled release solid dosage form  
according to claim 1 which comprises a granulation  
10 which is coated with a hydrophobic material to a weight  
gain from about 1% to about 20%.

15 16. The controlled release solid dosage form  
according to claim 14, wherein said hydrophobic  
material is selected from the group consisting of a  
cellulose ether, a cellulose ester and an  
alkylcellulose.

20 17. The controlled release solid dosage form  
according to claim 16 which is a tablet, at least part  
of a surface of said tablet being coated with a  
hydrophobic material to a weight gain from about 1 to  
about 20 percent, by weight.

25 18. The controlled release solid dosage form  
according to claim 17, wherein said mixture of  
sustained release excipient and medicament are coated  
with a hydrophobic material prior to tableting.

30 19. The controlled release solid dosage form  
according to claim 1 which is a tablet, said tablet  
further comprising a coating containing from about 10  
to about 40 percent of the total amount of said  
medicament included in said dosage form.

5           20. The controlled release solid dosage form according to claim 1 wherein the amount of albuterol is an amount equivalent to about 4 mg to about 16 mg of albuterol free base.

10           21. A method of preparing a controlled release solid dosage form comprising a medicament for oral administration, the method comprising  
            preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a  
15           gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum  
20           being from about 1:3 to about 3:1, and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and from about 1 to 90% by weight of a pharmaceutically acceptable hydrophobic material; and  
            adding an effective amount of a medicament  
25           thereto, such that a final product is obtained having a ratio of said medicament to said gelling agent from about 1:3 to about 1:8, such that a gel matrix is created when said formulation is exposed to environmental fluid and said formulation provides  
30           therapeutically effective blood levels of said medicament for at least 12 hours.

            22. The method of claim 21, further comprising  
35           tableting said mixture of said sustained release excipient and said medicament.

5           23. The method of claim 21, further comprising  
coating said tablets with a hydrophobic coating to a  
weight gain from about 1% to about 20%.

10           24. The method of claim 21, further comprising  
granulating said sustained release excipient with a  
hydrophobic material.

15           25. The method of claim 21, wherein said  
medicament is albuterol or a salt or derivative  
thereof.

          26. The method of claim 21, wherein said  
hydrophobic coating comprises ethylcellulose.

20           27. The method of claim 25, wherein the amount of  
albuterol is an amount equivalent to about 4 mg to  
about 16 mg of albuterol free base.

25           28. The method of claim 21, wherein said  
sustained release excipient comprises from about 10 to  
about 75 percent gelling agent, from about 0 to about  
90% hydrophobic material and from about 30 to about 75  
percent inert diluent.

30           29. The method of claim 21, wherein said  
formulation provides therapeutically effective blood  
levels of said medicament for at least 24 hours.

35           30. The method of claim 21, further comprising  
compressing the mixture of said sustained release  
excipient and said tablet into tablets.

5           31. The method of claim 21, wherein said  
medicament comprises a therapeutically effective dose  
of albuterol or salts and derivatives of the same.

10           32. A method of treating a patient with albuterol  
comprising,

          preparing a sustained release excipient comprising  
from about 10 to about 99 percent by weight of a  
gelling agent comprising a heteropolysaccharide gum and  
a homopolysaccharide gum capable of cross-linking said  
15       heteropolysaccharide gum when exposed to an  
environmental fluid, the ratio of said  
heteropolysaccharide gum to said homopolysaccharide gum  
being from about 1:3 to about 3:1, and from about 0 to  
about 89 percent by weight of an inert pharmaceutical  
20       diluent, and from about 1 to 90% by weight of a  
pharmaceutically acceptable hydrophobic material; and  
          adding an effective amount of a albuterol, or a  
salt or derivative thereof, to said sustained release  
excipient, such that a final product is obtained having  
25       a ratio of albuterol to said gelling agent from about  
1:3 to about 1:8, such that a gel matrix is created  
when said formulation is exposed to environmental fluid  
and said formulation provides therapeutically effective  
blood levels of albuterol for at least 12 hours.

30           adding an amount of albuterol effective to render  
a desired therapeutic effect;

          tableting the resultant mixture such that a final  
product is obtained having a ratio of albuterol to said  
gelling agent from about 1:3 to about 1:8, such that a  
35       gel matrix is created when said tablet is exposed to  
gastrointestinal fluid and said tablet provides  
therapeutically effective blood levels of albuterol;

5           and

          administering said tablet to a patient at a  
predetermined dosage interval from about 12 to about 24  
hours.

10           33. The method of claim 32, further comprising  
coating said tablets with a hydrophobic material to a  
weight gain from about 1% to about 20%.

15           34. The method of claim 32, further comprising  
preparing said formulation such that it provides  
therapeutically effective blood levels of said  
medicament for at least 24 hours.

20           35. The controlled release solid dosage form of  
claim 1 which, when orally administered to a patient,  
provides a medicament plasma concentration-time curve  
with an area under the curve, to infinity, ranging from  
about 89 to about 150 (ng-hours/ml).

25           36. The controlled release solid dosage form of  
claim 1 which, when orally administered to a fasting  
patient, provides a medicament plasma concentration-  
time curve with an area under the curve, to infinity,  
ranging from about 57 to about 157 (ng-hours/ml).

30           37. The controlled release solid dosage form of  
claim 1 which, when orally administered to a fed  
patient, provides a medicament plasma concentration-  
time curve with an area under the curve, to infinity,  
35           ranging from about 75 to about 162 (ng-hours/ml).

5           38. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a mean peak plasma concentration ranging from about 7 to about 12 ng/ml.

10           39. The controlled release solid dosage form of claim 1 which, when orally administered to a fasting patient, provides a mean peak plasma concentration ranging from about 4.5 to about 19 ng/ml.

15           40. The controlled release solid dosage form of claim 1 which, when orally administered to a fed patient, provides a mean peak plasma concentration ranging from about 6 to about 16 ng/ml.

20           41. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a time to mean peak plasma concentration ranging from about 3 to about 10 hours.

25           42. The controlled release solid dosage form of claim 1 which, when orally administered to a fasting patient, provides a time to mean peak plasma concentration ranging from about 3 to about 6 hours.

30           43. The controlled release solid dosage form of claim 1 which, when orally administered to a fed patient, provides a time to mean peak plasma concentration ranging from about 3 to about 8 hours.

5           44. The controlled release solid dosage form of  
claim 35 wherein the area under the plasma  
concentration curve, to infinity, ranges from about 112  
to about 129 (ng-hours/ml).

10           45. The controlled release solid dosage form of  
claim 38 wherein the mean peak plasma concentration  
ranges from about, 9.5 to about 12 ng.

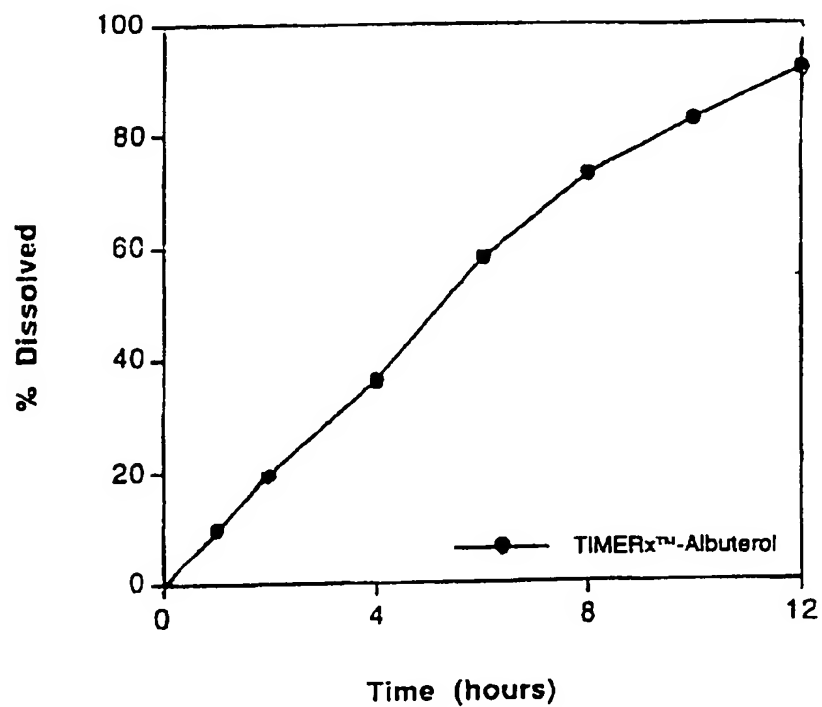
15           46. The controlled release solid dosage form of  
claim 42 wherein the time to mean peak plasma  
concentration ranges from about 3.5 to about 8 hours.

20           47. The controlled release solid dosage form of  
claim 1 which, when orally administered to a patient,  
provides a medicament plasma concentration-time curve  
wherein time to peak plasma concentration in a fasted  
patient divided by a time to peak plasma concentration  
in a fed patient ranges from about 0.50 to about 0.70.

25           48. The controlled release solid dosage form of  
claim 1 which, when orally administered to a patient,  
provides a medicament plasma concentration-time curve  
wherein peak plasma concentration in a fasted patient  
divided by peak plasma concentration in a fed patient  
30 ranges from about 0.90 to about 1.10.

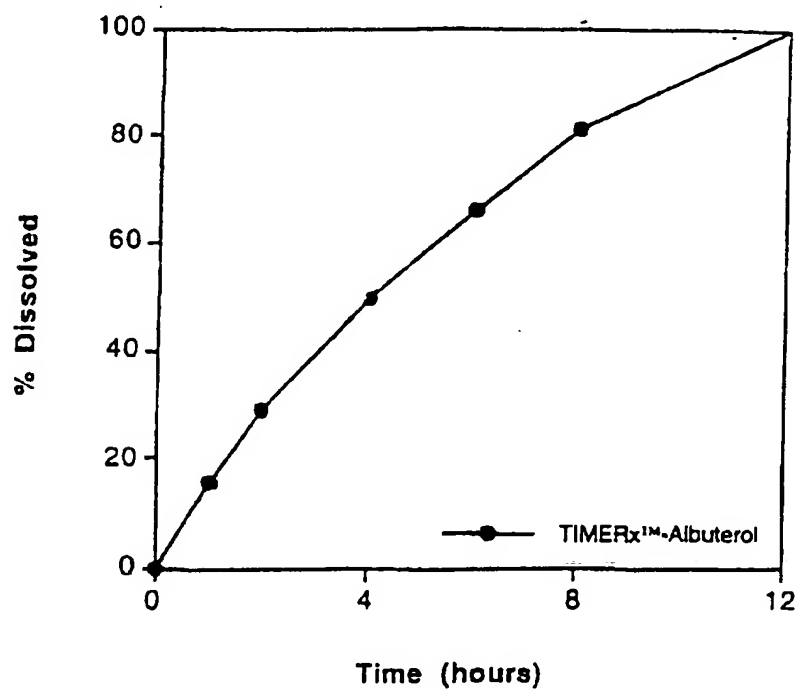
1/3

**FIGURE 1**  
**Albuterol Dissolution Profile**  
Type II - pH 1 Method - 50 rpm

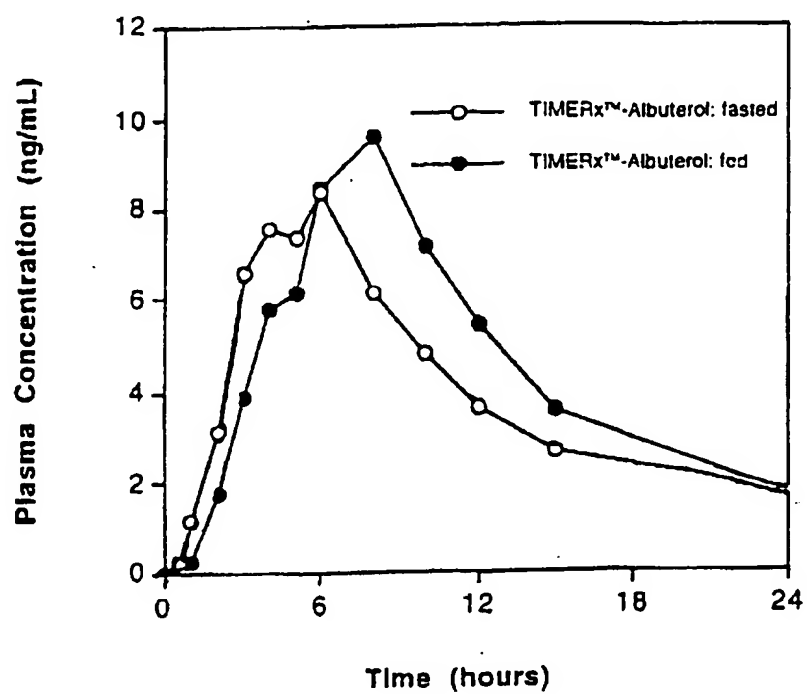




**FIGURE 2**  
**Albuterol Dissolution Profile**  
**Type III - pHΔ Method - 15 cpm**



**FIGURE 3**  
**Albuterol Plasma Profile**



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/17991

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/14, 9/22

US CL :424/457, 468, 488; 514/777, 778, 779, 780, 781, 964, 965

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/457, 468, 488; 514/777, 778, 779, 780, 781, 964, 965

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,455,046 (BAICHWAL) 03 October 1995, see claims 1-51.	1-48

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"A" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

24 JANUARY 1997

Date of mailing of the international search report

05 MAR 1997

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

NATHAN M. NUTTER sc

Telephone No. (703) 308-1235

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

☐ **BLACK BORDERS**

☒ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**

☒ **FADED TEXT OR DRAWING**

☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**

☐ **SKEWED/SLANTED IMAGES**

☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**

☐ **GRAY SCALE DOCUMENTS**

☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**

☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**

☐ **OTHER:** \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**